Thesis:

Secondary Shockable Rhythms: Prognosis in Cardiac Arrests with Initial Asystole or Pulseless Electrical Activity and Subsequent Shockable Rhythms

This report was prepared by
Andrew J. Thomas

Committee
Mohamud R. Daya (Advisor)
Rochelle Fu
Craig D. Newgard
Dana M. Zive

Department of Public Health & Preventive Medicine
School of Medicine
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, Oregon 97239-3098
USA

www.ohsu.edu/public-health/
Tel: (503) 494-8257
Fax: (503) 494-4981
E-mail: phpm@ohsu.edu

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Andrew J. Thomas

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Master's Thesis, September 2011

Department of Public Health and Preventive Medicine
School of Medicine
Oregon Health and Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of
Andrew J. Thomas
has been approved by:

Mentor / Advisor

Member

Member

Member

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Abstract

Context There are numerous potential benefits to better understanding the prognosis of victims of initially non-shockable cardiac arrests including changes to future resuscitation care guidelines.

Objective To evaluate whether out-of-hospital cardiac arrest outcomes for patients whose initial arrest rhythm is nonshockable improve or worsen with subsequent conversion to shockable rhythms.

Design, Setting, and Patients This study is a cohort design secondary analysis of the prospectively-collected Cardiac Arrest Epidemiologic Registry (Epistry) organized by the Resuscitation Outcomes Consortium (ROC) of all out-of-hospital cardiac arrests at eight North American sites (6 US and 2 Canadian) between December 1, 2005, to May 31, 2007, followed through hospital discharge. The investigational cohort is identified as all EMS-treated adult (18 and older) cardiac arrest patients who presented in non-shockable rhythms (Pulseless Electrical Activity, Asystole, or Automated External Defibrillator non-shockable) and were treated by emergency medical services (EMS) personnel and had a non-traumatic cause of arrest.

Main Outcome Measures Survival to hospital discharge.

Methods Simultaneous analysis of multiply-imputed and complete-case datasets by logistic regression. Multiple imputation was used to permit analysis of all cases including cases with incomplete ascertainment of one or more covariates.

Results A total of 6,662 adult atraumatic cardiac arrest cases found in non-shockable rhythms met our inclusion criteria and survival outcomes were known for 6,593 (98.96%) cases. Analysis of these data reveal survival to discharge in 2.69% of patients. In patients who later converted to shockable rhythms survival was 2.72% and in those who never converted to shockable rhythms survival was 2.68%, a statistically insignificant difference between these groups (two-tailed z-test, p = 0.9555). These results were similar after controlling for a set of potential confounders which were selected *a priori* to coincide with earlier research.

Conclusion The results of this research do not agree with several previous studies which found that out-of-hospital cardiac arrest survival differs when non-shockable rhythms convert to shockable rhythms during the course of treatment nor do they agree with studies which found the opposite – that conversion to shockable rhythms was detrimental to patient survival. Our results suggest that cardiac arrest patients fare similarly in terms of survival to hospital discharge regardless of converting to shockable rhythms at subsequent rhythm assessment.

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Chapter 1

Introduction & Background

1.1 Introduction

Cardiac arrest occurs when the heart muscle ceases its normal function of contraction to pump blood to organs and tissues throughout the body. There are numerous causes for cardiac arrest which include all manner of both injury and illness which if severe enough lead to total circulatory failure and cardiac arrest. Medical treatment for these injuries and illnesses has always focused on supporting the body's functions to reduce the probability of reaching this catastrophic conclusion.[1]

Every year in the United States it is estimated that there are over 155,000 cardiac arrests which occur outside hospital walls and without warning.[1,2] These so-called sudden cardiac arrests (SCA) or out-of-hospital cardiac arrests (OHCA) are uniquely frightening and traumatic to patients' loved ones.

As was previously mentioned, numerous medical conditions can ultimately lead to cardiac arrest and occasionally these conditions will go unrecognized or untreated resulting in SCA without prior medical intervention. Just as there are numerous causes of cardiac arrest, there are also numerous forms of cardiac arrest. The natural history of a cardiac arrest is as varied as the medical conditions which cause them. Contrary to its name, cardiac arrest is often not actually the stopping of the heart itself but rather the stopping (or the dramatic slowing) of the blood flow leaving the heart which is known as the cardiac output.

A heart beat consists of at least two crucial stages. There is the electrical signal (the "intent" to contract) followed by the mechanical contraction itself. Some cardiac arrests (such as ventricular tachycardia and ventricular fibrillation) exist as electrical dysfunction alone where the heart muscle is in fact following the "commands" it is given. Cardiac arrests of this type can often be corrected by shocking the heart with a sufficiently large dose of energy that the "electrical system" overloads and resets itself – ideally to a functional heart rhythm. Still other cardiac arrests (such as pulseless electrical activity and asystole) exist as mechanical dysfunction and may or may not have accompanying electrical problems as well. These cardiac arrests are not generally susceptible to correction by these electrical shocks (known as defibrillation countershocks).[3]

The current approach to treating cardiac arrest as recommended by both the International Liason Committee on Resuscitation (ILCOR) and the American Heart Association (AHA) is centered around 5 specific goals termed the "Chain of Survival". These goals are 1) early access including recognition of cardiac arrest access to emergency care (dialing 911), 2) early provision of CPR including untrained layperson CPR with 911 calltaker prompting, 3) early defibrillation of shockable rhythms, 4) early advanced life suport care, and 5) post-resuscitation prehospital and hospital care. This chain of survival not only identifies the key prognostic factors in survival of out-of-hospital cardiac arrest but also identifies the order of their priority in that each step is highly dependent on the quality of the previous steps.

1.2 Background

The nature of cardiac care and resuscitation has been shifting over the last 50 years and so has the nature of cardiac arrest itself.[4,5] Historically, the overwhelming success of defibrillation at correcting shockable forms of cardiac arrest has resulted in an strong emphasis on shockable arrest rhythms. This focus has had an impact on research and development efforts as defibrillator technology has been miniaturized and automated to create Automated External Defibrillators (AEDs) and pharmacotherapy research has focused largely on heart rhythm drugs to address ventricular dysrhythmias.[3] Similarly it has had an effect on clinical treatment decisions as patients in shockable rhythms are rarely declared dead in the field while non-shockable rhythms account for nearly all death in the field declarations.[3]

An obvious benefit of new prevention and treatment therapies has been shifting trends in cardiac arrest survival. A less obvious consequence however has been subtle trends in the characteristics of cardiac arrest encountered by emergency medical services. EMS systems have observed a steady decrease in the incidence of shockable rhythms in cardiac arrest.[6–8] This trend may be due to the increasing prevalence of implantable defibrillator devices and cardiac medications used to treat everything from hypertension to migraines. Alternative theories for this observed change in presenting rhythm include globally changing environmental and individual risk factors, earlier recognition and intervention for myocardial infarction (MI), and other factors both intrinsic to and independent from the pre-hospital EMS system.[6,8]

Unfortunately, historical events and the success of treating shockable rhythms has consipired against developing effective treatments for non-shockable rhythms. As a result, both PEA and asystole are often considered terminal rhythms. This may be in part due to the fact that these two rhythms often are the terminal rhythms of a cardiac arrest. In addition it is likely that low expectations for survival result in a self-perpetuating cycle – when low prognosis for survival is expected there is less motive to develop new treatments.

Historically there has been great emphasis upon evaluating survival rates of bystander-witnessed cardiac arrests with shockable rhythms. But some communities have improved their survival faster than others. There is some question as to what degree this might be due to the selection bias of more shockable-rhythm cardiac arrests being successfully treated by AICDs and AEDs prior to EMS personnel arriving on-scene.[3]

Recognizing the opportunity for improvement, both resuscitation researchers and EMS systems in recent years have begun focusing more attention on the non-shockable rhythms in hopes that greater survival can be achieved in this category as well.[3] Any improvement in survival is anticipated to have an increasing benefit in the future as the proportion of non-shockable cardiac arrest events trends upward.

Traditionally, both PEA and asystole have been though to possess a low probability of survival. However, in recent years as new emphasis has been placed on the delivery of high-quality cardiopulmonary resuscitation (CPR) gradually improving survival from non-shockable rhythms has been observed. It has long been believed that treatment of non-shockable rhythms (and in particular – asystole)[2] should focus on increasing cardiac muscle perfusion with CPR compressions and myocardial tissue excitability to encourage fibrillation which has a known remedy – defibrillation.[3] Similarly it has been believed that converting from non-shockable rhythms to shockable rhythms represented an improvement in patient condition and therefore an increased probability of survival.[3]

With recent advances in treatment such as improved CPR quality and post-resuscitation induced hypothermia focused on increasing the likelihood of positive neurologic outcomes[9][10], the window for entirely successful cardiac arrest resuscitation is widening.[3] With this comes an even greater opportunity for improved survival in the historically dismal category of non-shockable cardiac arrests. However one of the first steps to improving these outcomes is understanding if our current treatment strategy is effective. Critical evaluation of this issue has raised the question of whether or not the current strategy for treatment is based upon correct thinking. There are several explanations for this but perhaps the prevailing one is that non-shockable rhythms represent a more diverse constellation of medical conditions (compared to shockable rhythms) which may not benefit as much from traditional therapies and instead require specific identification and remediation before cardiac resuscitation can be achieved.[3]

To test the theory that conversion from non-shockable rhythms to shockable rhythms during the course of resuscitation represents an improvement in patient condition, researchers have examined the probability of survival as it depends on this rhythm conversion. In 2007, Hallstrom *et al.* published a manuscript in Resuscitation detailing retrospective analysis of data collected during the ASPIRE trial in the US and Canada. Their findings contradicted the previously-held belief that conversion to shockable rhythms represents an improved probability of survival. Surprising many observers, in this post-hoc study survival for patients who never developed shockable rhythms was over 8 times as high as for those who were initially non-shockable but later developed shockable rhythms. Even after adjusting for potentially confounding covariates they identified an odds ratio for survival of 0.18 ($p = 0.036$) for patients with subsequently shockable rhythms relative to those who did not convert to shockable rhythms.[11]

In 2008 two studies published independently by Herlitz *et al.*[12] (conducted in Sweden) and Kajino *et al.* (conducted in Japan)[13] demonstrated findings contrary to those reported by Hallstrom *et al.* – that subsequent conversion to shockable rhythms translated to improved survival from cardiac arrest relative to those patients who never received defibrillation shocks. Both studies were based on prospectively-collected cohort registry datasets and the findings were fairly consistent and did not change significantly after correcting for potential confounders. Both study authors raised questions and proposed several theories about their contrary results.[12,13]

The following year, Olasveengen *et al.* published the account of a study conducted in Oslo, Norway between 2003 and 2008. They examined all out-of-hospital cardiac arrests treated by Oslo EMS during that time period. They too concluded that the chances for survival improved significantly for patients found in non-shockable rhythms who later converted to shockable rhythms.

As the evidence appeared to confirm previous assumptions and some were beginning to question the results of the original Hallstrom paper[3] an in-hospital cardiac arrest study published by Peter Meaney and colleagues in the January, 2010 issue of Critical Care Medicine added to the confusion. They found a considerably higher survival in both PEA and asystole patients who had never converted to shockable rhythms relative to those who had converted. Moreover, this study examined multiple outcomes and found consistent results whether the outcome measured was return of spontaneous circulation (ROSC), 24-hour survival, survival to hospital discharge, or favorable neurologic outcome. Like the original Hallstrom study, the Meaney study was conducted in the United States which lends some to conclude that the substantial differences in cardiac arrest treatment and response between North America and Scandanavia & Japan which might be responsible for these confusingly contrary results. While the Meaney study made no attempt to control for potential confounders, none of the previous studies had drawn substantially different conclusions from their multivariate analyses than from their univariate ones.[14]

The characteristics and findings of each of these studies are outlined in Table 1.1. Their findings are also illustrated on the Forest plot marked Figure 1.1.

Author	Years (Pub.) Location(s)	Outcome Predictor	Odds Ratio	95% CI	Model Type
Hallstrom et al.	'04-'05 ('07)	Survival to Discharge	0.11	0.02–0.89	Univariate
	US and Canada	Shocks Delivered	0.18	0.08–0.92	Multivariate
Herlitz et al.	'90-'05 ('08)	1-Month Survival	2.2	1.88–2.66	Univariate
	Sweden	Shocks Delivered	1.96	1.49–2.56	Multivariate
Kajino et al.	'01-'05 ('08)	1-Month Survival	4.7	3.54–6.27	Univariate
	Japan	Shocks Delivered	4.3	2.8–6.7	Multivariate
Olasveengen et al.	'03-'08 ('09)	Survival to Discharge	3.33	1.35–8.24	Univariate
	Norway	Shocks Delivered	3.02	1.07–8.57	Multivariate
Meaney et al.	'99-'05 ('10)	Survival to Discharge	0.63	0.56–0.69	Univariate
	US	Subsequent VF/VT	n/a	n/a	Multivariate

Table 1.1: Characteristics of prior research studies

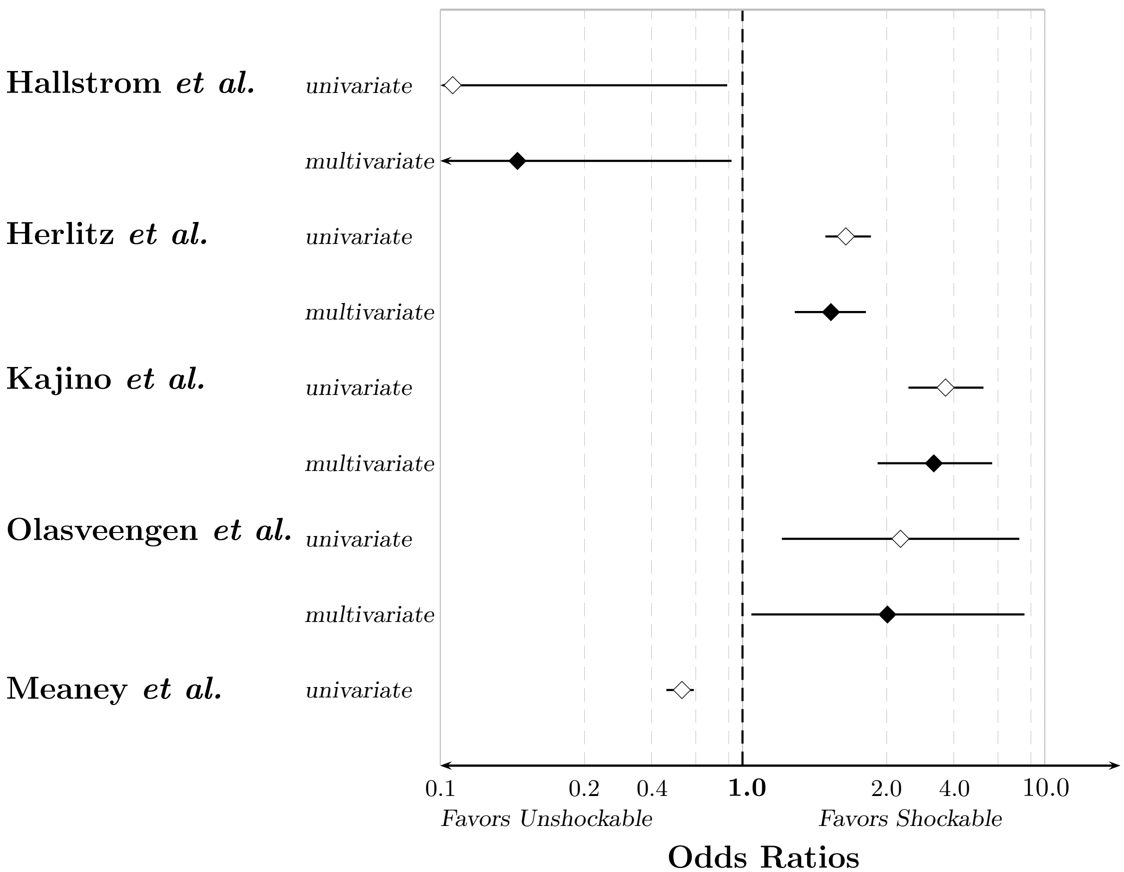

Figure 1.1: Forest plot of prior research
(Note: Meaney depicts in-hospital arrests.)

Beside EMS system differences, another hypothesis which might contribute to the observed differences between these studies is the length of time spent treating cardiac arrest in the prehospital setting. A situation may exist whereby cardiac arrests which do not convert to shockable rhythms have actually not been treated with CPR and drug therapy as long as those which do convert to shockable rhythms. In effect, some of these non-shockable rhythm arrests may have been terminated prematurely (relative to their potential) and those which are had less likelihood of converting to shockable rhythms. This would result in a bias toward the conclusion that asystole and PEA are terminal rhythms. However because the EMS system in Osaka does not permit termination of resuscitative efforts in the field, this explanation is in doubt.

For lack of adequate understanding and to explore potential reasons for these observed differences, more research is needed to parse out these complex issues. Should the question of prognosis for subsequently shockable rhythms be adequately answered it will likely contribute to the development of treatment recommendations which may benefit the survival of future victims of cardiac arrest.

Chapter 2

Methods

2.1 Institutional Review Board Approval

This study protocol has been approved by the Institutional Review Board at Oregon Health & Science University under study number IRB00007504 with an exemption from IRB review and approval in accordance with United States Department of Health & Human Services regulation 45CFR46.101(b)[4], research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if the sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

2.2 Objective & Specific Aims

The objective of this investigation is to answer the question of among victims of out-of-hospital cardiac arrest who are found in non-shockable cardiac rhythms whether subsequent conversion to shockable cardiac rhythms predicts a greater or lesser chance of survival to hospital discharge. Also implicit in this objective is answering the question regarding whether subsequent conversion to shockable rhythms represents an improvement to patient condition in OOHCA as was the previously-held expert consensus until recent years' research called this belief into question.

Specific aims of this study are:

1. Test the null hypothesis that there is no difference between the probability of survival of patients who convert to shockable rhythms and the probability of survival of those who do not experience this subsequent conversion. The alternative hypothesis is that patients who convert from non-shockable to shockable rhythms will have a different probability of survival than those who do not.

2. Test the above hypotheses using a statistical model to account for known and anticipated confounding factors including:

   (a) Age

   (b) Gender

   (c) Location of cardiac arrest (public vs. private)

   (d) Bystander & EMS-witnessed arrests

   (e) Bystander CPR & AED use

   (f) EMS response interval

   (g) ROC site (to adjust for variation due to local factors)

2.3 Data Source

The Resuscitation Outcomes Consortium (ROC) is a cooperative of North American resuscitation research centers designed primarily as a vehicle for conducting large-scale randomized controlled trials in the fields of both cardiac and trauma resuscitation. At present, the organization is comprised of[3,15–17] Among the particular challenges facing the organizers of ROC are the regulatory issues facing any interventional study group which operates under an exception from informed consent. Being a large multi-site organization, the ROC study group also faces the unique obstacle of operating in multiple communities with multiple layers of regulatory oversight from IRBs and funding partners.[18] The tradeoff however is that by collaborating on such a large-scale project, those involved may conduct research with sample sizes sufficiently-large enough to answer important questions about resuscitation – research which previously was not feasible for many reasons.

The ROC is supported by a series of cooperative agreements to 10 regional clinical centers and one Data Coordinating Center (5U01 HL077863 - University of Washington Data Coordinating Center, HL077865 - University of Iowa, HL077866 - Medical College of Wisconsin, HL077867 - University of Washington, HL077871 - University of Pittsburgh, HL077872 - St. Michael's Hospital, HL077873 - Oregon Health and Science

University, HL077881 - University of Alabama at Birmingham, HL077885 - Ottawa Health Research Institute, HL077887 - University of Texas SW Medical Ctr/Dallas, HL077908 - University of California San Diego) from the National Heart, Lung and Blood Institute in partnership with the National Institute of Neurological Disorders and Stroke, U.S. Army Medical Research & Material Command, The Canadian Institutes of Health Research (CIHR) – Institute of Circulatory and Respiratory Health, Defence Research and Development Canada and the Heart, Stroke Foundation of Canada and the American Heart Association.

One necessary component for conducting these large-scale multicenter trials was the creation of a data collection system both consistent and reliable enough to be statistically defensible and satisfy the requirements of all regulatory bodies and funding partners. It was decided that this data collection system would be geared toward broad collection of data which, in addition to the serving the interventional trials, allows surveillance to follow secular trends as well as the conduct of hypothesis-generating observational research studies. The name Epistry was chosen as an truncation of "Epidemiologic Registry" and two separate databases were created – one for severe trauma and one for cardiac resuscitation.[(15)]

While all member sites participate in the Epistry data collection, not all have chosen to distribute their data to other sites. The participating centers include the greater metropolitan regions of four cities within the United States and Canada (Dallas-Fort Worth, Texas; Milwaukie, Wisconsin; Pittsburgh, Pennsylvania; Portland, Oregon) as well as two statewide networks (based in Birmingham, Alabama and Falls City, Iowa) and two provincial networks (based in Vancouver, British Columbia and Ottawa, Ontario [a]). Resuscitation research centers at each of these locations both participated in the ROC Epistry of cardiac arrests between 2005 and 2007 and subsequently local research coordinators elected to release their data for the purpose of secondary analyses by investigators at other sites [b].

2.4 Study Design

The design of this study is influenced largely by the characteristics of the data source which was collected for the purpose of prior research as described previously in the ***Data Source*** section. The limitations introduced by this data source will be discussed later in the ***Study Strengths and Limitations*** section of this publication.

[a]British Columbia's network is province-wide while Ontario represents a collection of cities participating with the Ottawa ROC site.

[b]Though they are actively-participating ROC sites, both Seattle-King County, Washington and the Ontario cities affiliated with the Toronto ROC site have opted not to participate in this Epistry-local analysis.

This investigation amounts to a cohort study from secondary analysis of prospectively-collected data. Though organizers strive to have complete ascertainment of cases within their sites, there may be rare cases of out-of-hospital cardiac arrest which are not captured in this dataset for various reasons. Additionally, studies using these data generally aim to generalize their conclusions to cardiac arrests falling outside the geographic and temporal boundaries of this study. The cases included in this study are a census of all EMS-treated cardiac arrests occurring within these boundaries of time and geography which is believed to accurately represent the state of cardiac arrest in similar communities elsewhere.

2.5 Setting & Population

The setting for this study includes the greater metropolitan regions of the four cities in the United States and Canada and the four state and provincial networks (Alabama, Iowa, British Columbia, & Ontario) which were previously described. The potential patient population for this study can be classified as all individuals susceptible to experiencing out-of-hospital cardiac arrest within the geographic regions described above. In theory this would include all human beings however there are some constraints to this generalization which are pertinent to consideration of potential systematic error. Certain institutionalized populations (including of course hospitalized patients) do not receive care through the ordinary emergency medical system and are therefore not considered in these data. Additionally, some communities or jurisdictions within these geographic regions are served by agencies who did not participate in this study and are similarly not included in these data.

Previous papers have described the variation which exists in EMS system design, response structure and capabilities, and staffing between each of these participating ROC sites.[17] However the variation in EMS treatment algorithms, strategies of resuscitation and termination of resuscitation, or organizational culture factors affecting resuscitation efforts are less well described in the published literature. Nonetheless, between the member sites of ROC there is reason to believe that there exists a wide degree of variation in all of these features.[17,19]

2.6 Selection of Cases

Cases include all adult (aged 18 and up) victims of cardiac arrest who were treated by participating EMS response agencies in the above-described geographic areas from December 1, 2005 through May 31, 2007. Patients were excluded if their arrest was documented to be related to serious traumatic injury, and if their resuscitation was

Figure 2.1: Participating ROC member sites

terminated prematurely due to patient or family requests (such as discovery of a Do Not Attempt Resuscitation order). Within this time interval and with these additional constraints this dataset is believed to be a near-complete census of all such events occurring in these geographic regions.[20–22]

2.7 Outcomes

The primary outcome of interest from several previous studies was survival to hospital discharge. As this has become the *de facto* standard for measuring cardiac arrest survival with both economically and clinically relevant positive outcomes this has been selected as our primary outcome for this study. Other previous studies chose to use survival to 30 days post-arrest however these data were not consistently available from our dataset preventing their use as an outcome for this study.

Another logical outcome of interest is survival to hospital admission representing the out-of-hospital and emergency departments' success at treating the cardiac arrest. Unfortunately these data were optional fields for the staff of the original study for which these data were collected and resultingly there is no assurance that these data were collected consistently at all participating sites. Therefore we have chosen not to attempt this analysis from these data lest erroneous conclusions be drawn from its results due to the systematic bias of data collection.

Survival is therefore classified as hospital record-identified live discharge from the hospital while any mortality prior to discharge was defined as non-survival. These data were mandatory data entry elements and are therefore available in our dataset.

2.8 Model Selection

As described previously, the consensus model consists of covariates recommended by the Utstein criteria and with reasonable consensus between this study and previously-published investigations. Model 2 represents our expanded model which considers each of the components of bystander resuscitation available in our dataset. These variables were selected *a priori* based on supporting evidence from earlier studies.

Variable	Name	Type *Values*	Description
Survival to Discharge	surv	categorical nominal *yes, no*	The official determination of survival to hospital discharge.
Patient Disposition	pdisp	categorical nominal *died, transported, alive/no transport*	The EMS report indicated disposition of on-scene care.

Table 2.1: Characteristics of original source variables contributing to the outcome designation and verification.

2.9 Variables & Selection

Confounding variables are included in the model based on significance identified by previous investigators. A more proximate influence on this study's design is something known to the industry as the Utstein data elements. In June of 1990, members of several major professional organizations with interests in cardiovascular resuscitation held a summit at Utstein Abbey in Stavanger, Norway. During this and a subsequent meeting in Surrey, England, these delegates developed a consensus on terminology, definitions, and key elements for uniform data collection pertaining to out-of-hospital cardiac arrest. Subsequent meetings of resuscitation experts have reiterated the importance of these data elements while simultaneously adding to and improving the list. Among these key data elements are initial cardiac rhythm, EMS response time, public location of arrest, bystander witnessed arrests, bystander CPR, and more recently the use of public access AEDs by layperson bystanders.[1,20,21,23–25] Because these important measurable confounders have been established by prior research and consensus opinion, variable selection methods are not employed in this study.

Initial Rhythm

The investigational cohorts are classified with regard to their initial EMS-assessed cardiac arrest rhythm. Due to variation in EMS system capabilities, deployment models, and resuscitative strategies there is no consistent way to compare specific initial rhythm distributions between participating sites. Due to the relative prevalence of basic life support-level EMS staffing particularly among crews of first-arriving EMS units the AED-assessed shockable rhythm was combined with EKG-diagnosed ventricular fibrillation and ventricular tachycardia to compose the shockable rhythm group. AED-assessed non-shockable rhythm was similarly combined with asystole and pulseless electrical activity to form the non-shockable rhythm cohorts.

Within the non-shockable group, those converting to shockable rhythms were identified by the absence of shockable rhythms upon first assessment combined with the presence of any shocks later in the course of resuscitation to form the SHOCK cohort. Similarly, the NO SHOCK cohort was composed of those receiving no subsequent shocks and therefore presumably remaining in non-shockable rhythms. The use of subsequent shocks as a surrogate for conversion to shockable rhythms was an *a priori* decision which was made for two reasons. First there exists substantial prior precedent for this surrogacy and its consistent use would improve comparison with prior studies. Moreover, we were logistically limited because our dataset did not contain any other means (such as continuous ECG data) which might have allowed more accurate determination of subsequent rhythms.[26]

Age & Gender

By standard convention and with strong evidence of support from both the Utstein consesus criteria and prior studies, we incorporated both age in years and gender as predictors in our multivariate analyses. There is substantial evidence to suggest that the distribution of both risk factors and causes for cardiac arrest differs between genders which lends at least partial explanation to the observed disparate rates of resuscitation as well. Similarly, age has been seen to be a strong predictor of cardiac arrest and a predictor of decreasing probability of successful resuscitation.

Bystander Variables

Bystander Witnessed As cardiac arrest represents a failure to perfuse bodily tissues and organs with sufficient oxygen and nutrients to sustain life, timely recognition of this state is crucial to ensuring maximal probability of favorable outcomes – both in terms of survival and neurologic status. The optimal condition for recognition of course is a witnessed arrest where notification of an emergency response system and pre-arrival resuscitation can be provided immediately. If an arrest is not witnessed (or heard) then desired condition for optimal survival is the minimal delay possible before recognition of the arrest.[19,27]

CPR Attempted Bystander CPR has long been emphasized as a promising means of improving survival in out-of-hospital cardiac arrest.[28,29] While some studies have not demonstrated the expected benefits of bystander CPR in some or all patient subgroups,[19,30,31] one large meta-analysis by *Sasson et al.* determined that bystander CPR was consistently beneficial for all-rhythm cardiac arrests.[29,32]

AED Application Bystander AED use has been included because some earlier studies have suggested that AED application is only beneficial if it reaches the patient during the electrical (e.g. – shockable initial rhythm) phase of arrest. However there is some disagreement on this matter. While it is conceivable that bystander application of an AED may be responsible for improving odds of survival (even in non-shockable rhythms) because many current AED devices present voice prompts to encourage quality CPR performance.[33,34] An alternative hypothesis however suggests that in patients found in non-shockable rhythms, AED use necessitates pauses in CPR to allow for rhythm analysis which in patients who will not be receiving a defibrillation results in detrimental effects including ceased coronary perfusion and rapidly diminishing cerebral perfusion pressure.[33,35]

AED Shock Delivery AED shock delivery is also an important predictor because it indicates that an AED reached the patient during the electrical phase of the arrest. If the patient is non-shockable upon EMS arrival, as they must be in order to be included in this analysis, the presence of prior AED shocks serves to indicate that the arrest was recognized during the electrical phase and thus was presumably a recent arrest with a higher chance of survival than one with considerably delayed recognition.[33,36]

Public Location

As mentioned previously, the optimal condition for recognition of an arrest is one where resuscitation can be provided immediately. In public places not only is a witnessed arrest more likely but recognition is likely to happen sooner than in the privacy of one's own home. These factors have previously been suggested to be predictive for improved survival.[19,27,37]

EMS Response Variables

EMS Response Interval This likely somewhat overlaps the discussion of bystander resuscitation as many cardiac arrests still occur without bystander intervention prior to EMS arrival. In these situations, arrival of EMS responders marks the first initiation of resuscitative efforts. Shorter time intervals from arrest to initiation of resuscitation leads to decreased duration of hypoperfusion and reduced cellular damage to the brain and other vital organs. This in turn has shown to lead to increased probability of survival to hospital discharge in numerous studies.[37,38]

EMS Witnessed Arrests Perhaps the most extreme example of the value of EMS response interval is the case of EMS-witnessed arrests which have been shown to have a very significant positive effect on patient outcomes.[39]

Known Causes

If a patient is known to have died from an asphyxiation type of cardiac arrest there may be sufficient record documenting this fact. Nonetheless, there is a reasonable likelihood that many asphyxiation type arrests were not known and were therefore not documented as such. Other presumed causes of arrest are equally problematic as formal autopsies are often not performed on individuals who die without evidence of trauma. For this reason use of subsets of cause of arrest are not included as predictors in our model but the subsets 'No Known Cause' (presumed to be of cardiac cause) and 'Suspected Hanging/Drowning/Asphyxia' are presented as independent substrata for consideration.[2]

ROC Site Variation

The importance of taking into consideration both local and regional variation has been demonstrated multiple times. This fact is particularly evident when comparing outcomes from multi-site studies like the ROC epistry group as illustrated by Graham Nichol *et al.* in their 2008 paper for JAMA. Both the incidence and outcomes vary significantly between each of the participating ROC sites.[17,19] Some of these observed differences are no doubt due to the high degree of variation in terms of the staffing, training, quality improvement and assurance, call volume, and local protocols and practices of the EMS systems involved.[17,19] However it is impossible to discount the possibility that some of the variation in patient outcomes may be linked to the varied capabilities and treatment strategies of the hospitals to which the EMS systems transport their patients.[40]

Other Considered Variables

Historically it was understood that EMS response interval was an important predictor of survial because treatments such as defibrillation and CPR were rarely provided by bystanders. Nonetheless, as both educational and technological changes have allowed laypeople to provide these life-saving treatments, EMS response interval has maintained its importance as a predictor of mortality (shorter response intervals are better).[41] Perhaps surprisingly however, EMS transport interval (and by analogy – total EMS interval) has never been a consistent predictor of survival. There may be some special cases of cardiac arrest which benefit from prompt arrival at the hospital however as the vast majority of cardiac arrest survivors are resuscitated from shockable rhythms and these patients benefit from quality CPR and defibrillation followed by stabilizing treatment to prevent rearresting enroute to the hospital.[38,42] One study by Michael Cudnik and colleagues even pointed to the possibility that transport to further hospitals (with on average, greater resources and capabilities) resulted in better patient outcomes.[42] A related paper published by Callaway *et al.* described the lack of an association between specific receiving hospital characteristics and patient outcomes suggesting that no single factor is responsible for the improved outcomes observed at tertiary hospitals with resuscitation center capabilities.[43]

Interactions

Statistical interaction is always a possibility and may conceivably represent a true effect measure modification however none of the previous investigators which our study aims to follow have considered interactions in their model. Investigation of interaction terms may distract from the stated goal of examining the relationship between the primary predictor of subsequent shocks in initially non-shockable cardiac arrests and survival to hospital discharge. More importantly, inclusion of interaction terms can further complicate and confound the interpretation of the model as a whole or even the relationship of the primary predictor. Until the other questions of this particular relationship (such as magnitude and even direction) are settled we feel it is premature to include interaction terms in the model which would only serve to further complicate the analysis and limit comparisons with earlier research.

2.10 Missing Data

Cases possessing several missing variables were anticipated as the original data collection was not conducted specifically for the purposes of this study and some locations had different success with reporting optional variables. Furthermore, some variables were not recorded in the original documentation for certain cases resulting in difficulty in their ascertainment. Nonetheless, the effects of these covariates on the final outcome were expected to be substantial and any analysis without their consideration would be both suspect and difficult to compare to prior studies possessing more complete ascertainment.

In order to address the missing data the investigators had several options. The method employed by many previous studies, known as a complete case analysis, where cases

Author	Sample Size	Incomplete Cases	Incomplete Case %	Method
Hallstrom et al.	738	0 *	0% *	N/A
Herlitz et al.	22,465	5,986	26.7%	CCA
Kajino et al.	11,766	0 *	0% *	N/A
Olasveengen et al.	753	2	0.3%	CCA
Meaney et al.	55,701[†]	3,628[†]	6.5% [†]	CCA

[a]Insufficient information available to determine missing cases or methods.
[b]Includes all rhythms (shockable & non-shockable).

Table 2.2: Summary of missing data from prior research. (CCA = Complete Case Analysis)

Variable	Name	Missing Cases (%)
Survival	survival	1.0%
Shocks	shocks	0.0%
Age	ageyr	0.0%
Gender	sexp	0.1%
Public Location	locpub	0.1%
Witness	witbys	19.8%
Bystander Resuscitation	bresus	12.5%
Bystander CPR	cpratt	12.5%[a]
Bystander AED	aedapp	12.5%[a]
Bystander Shocks	aedshk	39.6%[a]
EMS Witnessed	witems	0.0%
Response Time	respint	2.9%
ROC Site	asite	0.0%

Table 2.3: Characteristics of our missing data

possessing incomplete data are excluded from analysis presented several concerns.[2] Such analyses are prone to the introduction of bias resulting from patterns in the censure of incomplete observations or in the missing values themselves. Because this method has been used in previous studies, these investigators chose to retain a complete case analysis for the purpose of comparison with prior studies and to validate our imputation methods.

The complete case analysis utilizing the consensus model was hindered by exclusion of 29.1% of its cases due to possessing at least one missing value. The expanded model was even more restrictive with 39.8% of cases possessing missing values. These investigators wished to make use of the cases with only partial data ascertainment. This is favorable because it reduces the likelihood of producing the above-mentioned bias but also because it will increase the effective sample size potentially reducing the standard error and thereby narrowing the confidence intervals. All cases for which the initial rhythm type (shockable or non-shockable) and the outcome (survival to discharge) in addition the exposure (subsequent shocks) were known could be subjected to univariate analysis. However in previous studies, the above-described covariates were found to present a substantial risk of confounding in this type of univariate analysis.

A number of statistical techniques have been developed to address this need for multivariate analyses of data possessing incomplete observations. Among those techniques, multiple imputation was selected for several reasons. First, multiple imputation is well-known and is gaining acceptability among researchers. Secondly, multiple imputation has become very accessible thanks to the development of new software tools (including IVEware and the built-in SAS procedures MI and MIANALYZE) which allow fast and reliable deployment of this technique. And lastly, multiple imputation has been shown to produce less-biased estimates than other methods of handling incomplete multivariate data.[2] For more background on imputation, see A.1.

2.11 Data Quality Control

These data were collected by individual sites participating in the Resuscitation Outcomes Consortium. The collection and recording of data was performed in accordance with the guidelines set forth in the ROC Epistry Manual of Operations which specified instructions for both mandatory and optional data. All of our selected variables were mandatory data points and as such near-complete ascertainment of cases was anticipated. The Resuscitation Outcomes Consortium's Data Coordinating Center (DCC) is charged with monitoring and performing random-selection data quality audits from each site. The ROC data entry system, a secure online data entry portal, also possesses significant engineering controls to prevent the entry of nonfactual or contradictory information. These engineering controls include internal cross-checking which permit only plausible predetermined responses and disallow any internally inconsistent entries.[15]

Additional data quality checks were performed by evaluating the distribution of continuous variables to identify potentially erroneous values which were designated as missing values in the analysis dataset. Similarly, categorical data values which were incomplete, nonsensical, or conflicting with one-another were designated as missing in our analysis dataset.

2.12 Data Modifications

The final analyses were conducted with a modified dataset composed of data obtained from the original raw dataset provided by the Data Coordinating Center. The final data elements included both composite and computed data derived from that raw dataset.

Computed data were used for response interval. The start time was the "aligned" dispatch time and the end time was the "aligned" on-scene time of the first arriving response unit. Aligned times indicate that they were coordinated during data entry to a single time source.

Similarly nominal categorical variables were composited to generate fewer discrete categories for the purpose of analysis. Specifically for Initial EMS Rhythm: 'Asystole'; 'PEA'; and 'Nonshockable by AED' became "non-shockable" while the values 'Ventricular Fibrillation'; 'Ventricular Tachycardia'; and 'Shockable by AED' were provided by the DCC as simply “VF/VT/shockable”.

The last step in the generation of the final analytical dataset was the removal of all remaining raw variables not used in the model. This step permitted faster computation and simpler visualization of the dataset during analysis.

Predictors used in the final model possess the following characteristics described in Table 2.4.

2.13 Statistical Power

Being that this research consists of a secondary analysis of prospective data which has been previously collected, these investigators are limited by the constraints of the data recorded therein. Most notably, the sample size is constrained to only the cases which were recorded by earlier researchers during the afforementioned time interval. Given this constraint, it makes little sense to discuss the issue of sample size in conjunction with statistical power calculations. Instead we will use the related notion of effect size to discuss the statistical power of our study given the fixed sample size.

These investigators conducted *a priori* power calculations in order to evaluate the merit of conducting this study with the available data given their fixed and limited sample size. These power calculations were based on the assumptions of previously published covariate correlations. In order to err on the side of caution, no accounting was made for potential statistical interactions between the covariates by reducing the combined correlation. Instead the previously identified correlations were simply summed to calculate our best estimate of the potential covariate correlation of $r = 0.1123$ for use in the power calculations. C omputations were performed with version 11.0 of the PASS (Power and Sample Size) software published by the NCSS corporation.

Table 2.5 displays the results of the power and effect size calculations which have been bracketed in acknowledgement of the fact that there was a relatively large degree of uncertainty regarding the magnitude of the covariate correlations. As can be seen from these power calculation results, the power of this study is adequate to detect effect sizes much smaller than the published point estimates described earlier in Table 1.1.

2.14 Statistical Analysis

Prior to analysis, as described previously, the data were processed into their final formats and analyzed for distribution type and completeness. Following this preprocess-

Variable	Name	Type *Values*	Description
Age	agep	continuous *range of ages*	Patient's age in years.
Gender	sexp	categorical nominal *male, female, other/unk.*	EMS or hospital record-indicated gender.
Public Location	locpub	categorical nominal *yes, no, unknown*	EMS report indicates the arrest occurred in a public location.
Witness	witbys	categorical nominal *yes, no, unknown*	EMS report indicates a bystander-witnessed (or heard) arrest.
Bystander CPR[a]	cpratt	categorical nominal *yes, no, unknown*	EMS report indicates bystanders provided CPR prior to EMS arrival.[a]
Bystander AED[a]	aedapp	categorical nominal *yes, no, unknown*	EMS report indicates bystanders applied an AED prior to EMS arrival.
Bystander AED[a]	aedshk	categorical nominal *yes, no, unknown*	EMS report indicates bystanders delivered an AED shock prior to EMS arrival.
Bystander Resuscitation[b]	bresus	categorical nominal *yes, no, unknown*	Any combination of CPR, AED, and AED Shocks.
EMS Witnessed	witems	categorical nominal *yes, no, unknown*	EMS report indicates EMS witnessed arrest.
Response Interval	respint	continuous (time) *number of seconds*	Time from dispatch to first EMS apparatus arrival.
Site ID	site	categorical nominal *Site Number 1 – 8*	ROC site reporting each case.

Table 2.4: Predictors used in the final models

Sample Size	Odds Ratio	Power
4,725*	1.10	0.069
	1.25	0.202
	1.50	0.546
	2.00	0.953
	2.50	0.998
	3.00	1.000
6,662†	1.10	0.080
	1.25	0.260
	1.50	0.680
	2.00	0.989
	2.50	0.999
	3.00	1.000

Table 2.5: Results from the power and effects size calculations using both complete* cases and maximum potential† number of observations using multiple imputation to compensate for missing data both with a range of effect sizes (OR = 1.1 – 3.0) to allow for uncertainty in covariate correlations.

ing, two distinct datasets were constructed. The first dataset – used for our complete case analyses – consisted of all conforming observations available from our data source with the missing observations left intact. The second dataset – used for our imputation-based analyses – was generated by multiple imputation. We performed 10 iterations with 10 imputations using the IVEware Version 0.2 software package (University of Michigan, 2010) in order to generate our 10 distinct imputed datasets.

Each dataset (both complete-case and imputed) was subjected to the same three statistical analyses. In the first analysis phase, univariate analysis was conducted on each of the predictor variables using logistic regression to determine their univariate prediction for survival. For the complete-case dataset, cases missing the predictor variable of interest were excluded from these analyses.

During the univariate analyses, the datasets were subjected to a series of assessments to determine the individual effects of each predictor variable. All binary categorical predictors were evaluated using Fisher's exact tests. Continuous variables were evaluated using simple logistic regression. All p-values were 2-sided and an alpha of 0.05 was selected for determining statistical significance. Odds ratios and 95% confidence intervals were calculated.

The second phase of statistical analysis was multivariate consideration utilizing what this paper refers to as the "consensus" model as it shares most of its covariates with models used in prior research. This consensus model (Model 1) was selected for maximum comparability of our findings to prior (and hopefully future) research. For the complete-case dataset, cases missing any of the predictor variables of interest were excluded from analysis.

The third and final phase of analysis consisted of the construction of a maximally multivariate model (Model 2) from all presumed predictors available in our dataset. This new multivariate model was presented for analysis alongside the original model for two reasons. The first reason for this simultaneous analysis strategy is one of prior precedent – as mentioned in the variable selection section above, previous studies have been conducted with similar models and excluding available predictors will limit the comparability of this study's results. Another reason for utilizing the original model in our analysis is that the intent of this study is not to determine the effect of each covariate but rather specifically to determine the effect of subsequent conversion to shockable rhythms on survival. As such, confusion about which covariate is responsible for the observed effect is inconsequential to answering our question of interest so long as complete separation does not prevent such interpretation.

Multivariate logistic regression was employed to evaluate the effect of subsequent conversion to shockable rhythms with regard to the combined effects of the covariates in each of the models. Odds ratios were calculated from the regression model coefficients. The Hosmer-Lemeshow Goodness of Fit test was used to quantify the quality of fit of each of the regression models. The receiver operating characteristic curve was also generated to evaluate the predictive ability of the models.

All statistical analyses were conducted using SAS version 9.22 published by SAS Institute Incorporated.

Chapter 3

Results

3.1 Population Characteristics

Previous publications from the Resuscitation Outcomes Consortium investigators have described in great detail both the general populations and the specific cardiac arrest populations of the ROC member regions.[17,19] Rather than repeating these discussions we will focus on the unique aspects of the cohort represented in these data. Figure 3.1 describes the breakdown of cases in the overall database using a modified Utstein template.

3.2 Distributions of Independent Variables

In order to understand both the similarities and differences between each of the three major divisions of cases we will examine the distributions of covariates within each group. Table 3.2 displays the key covariates and their respective distributions across these three groups. Note that the initially shockable group is being offered purely as a reference as it is not formally a part of this analysis as possessing an initially shockable rhythm was an exclusion criterion for this study.

There were a total of 6,662 cases meeting our inclusion criteria of which 1,252 were subsequently shocked and were assigned to the SHOCK cohort while 5,410 received no shocks and were assigned to the NO SHOCK cohort. Survival outcomes were known for

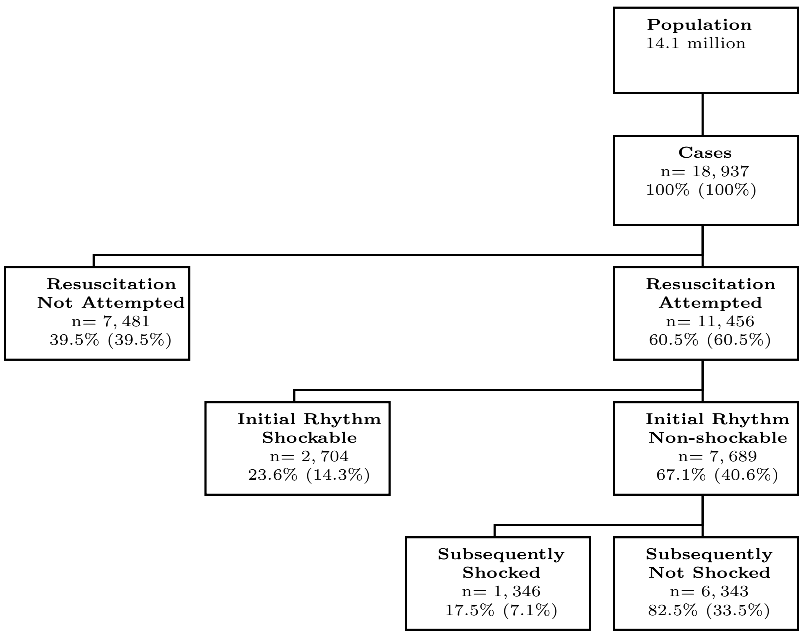

Figure 3.1: Case selection by modified Utstein template. (Note: Not all cases were included in analyses due to age and trauma-related death exclusion criteria.)

1,242 of the SHOCK cohort and 5,351 of the NO SHOCK cohort leaving an unknown outcome in 69 (1.04%) cases.

Table 3.1: Distribution of independent variables

Covariate	Initially Shockable[a]	SHOCK	NO SHOCK
Gender			
Male	1,935 (75.7%)	822 (65.7%)	3,236 (59.8%)
Female	617 (24.1%)	430 (34.3%)	2,168 (40.1%)
Age			
18–29	50 (2.0%)	39 (3.1%)	208 (3.8%)
30–39	92 (3.6%)	56 (4.5%)	297 (5.5%)
40–49	334 (13.1%)	129 (10.3%)	612 (11.3%)
50–59	579 (22.7%)	245 (19.6%)	934 (17.3%)
60–69	576 (22.5%)	230 (18.4%)	973 (18.0%)
70–79	546 (21.4%)	288 (23.0%)	1,248 (23.1%)
80–90	379 (14.8%)	265 (21.2%)	1,138 (21.0%)
Witnessed Arrest			
Bystander	1,517 (59.4%)	528 (42.2%)	1,584 (29.3%)
EMS	214 (8.4%)	103 (8.2%)	490 (9.1%)
Bystander Resuscitation			
Any	1,013 (39.6%)	377 (30.1%)	1,526 (28.2%)
CPR Attempted	992 (75.6%)	372 (72.1%)	1,493 (67.3%)
AED Applied	38 (2.9%)	30 (5.8%)	75 (3.4%)
AED Shocks	33 (86.8%)	20 (66.7%)	26 (34.2%)

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Table 3.1 – continued from previous page

Covariate	Initially Shockable[a]	SHOCK	NO SHOCK
EMS Response Time			
$\leq$ 4 minutes	1,177 (46.0%)	502 (40.1%)	2,269 (41.9%)
$>$ 4 minutes	1,102 (43.1%)	604 (48.2%)	2,504 (46.3%)
ROC Site			
Site 1	144 (5.6%)	106 (8.5%)	374 (6.9%)
Site 2	376 (14.7%)	157 (12.5%)	549 (10.1%)
Site 3	219 (8.6%)	144 (11.5%)	654 (12.1%)
Site 4	98 (3.8%)	23 (1.8%)	215 (4.0%)
Site 5	248 (9.7%)	101 (8.1%)	712 (13.2%)
Site 6	621 (24.3%)	319 (25.5%)	1,163 (21.5%)
Site 7	194 (7.6%)	127 (10.1%)	316 (5.8%)
Site 8	656 (25.7%)	275 (22.0%)	1,427 (26.4%)
Final Vital Status			
Survived to Discharge	515 (20.1%)	34 (2.7%)	145 (2.7%)
Died Prior to Discharge	1,982 (77.5%)	1,208 (96.5%)	5,206 (96.2%)

[a]Population characteristics of Initially Shockable group being offered purely for comparison, this group was included in the imputation model however was not a part of the subsequent analysis.

	Survived	Died		
Shock	34	1,208	1,242	*2.74 %*
No Shock	143	5,206	5,349	*2.67 %*
	177	6,414	**6,591**	
	19.21 %	*18.83 %*		

Table 3.2: Case outcomes by subsequent shocks

3.3 Outcomes

At first glance the data show a very slight increase in relative survival for cases of cardiac arrest found by EMS in non-shockable rhythms but later converting to shockable rhythms (the SHOCK group) relative to those who never converted to shockable rhythms (the NO SHOCK group). These results are displayed in Table 3.2.

3.4 Imputed Data Analysis

The first stage of analysis was the examination of all available cases (n=6,662) through the process of multiple imputation as described in the Methods section as well as the appendix A. This process permitted analysis of all cases for which initial rhythm and subsequent shocks data were available.

Univariate Analysis

In univariate analysis of imputed cases, each of the covariates were tested as predictors for survival to hospital discharge in separate univariate logistic regression models for each of the ten imputed datasets. These results were then combined to create univariate composite point estimates and confidence intervals for each covariate. The results from these analyses are displayed in Table 3.3 alongside those from the complete case analysis.

Multivariate Analysis

In multivariate analysis of imputed cases, each of the covariates were added as predictors for survival to hospital discharge in separate multivariate logistic regression models for each of the ten imputed datasets. These results were then combined to

Covariate	Univariate Analyses	
	Imputed Cases	Complete Cases
Shocks Delivered	1.03 (0.71–1.50)	1.01 (0.69–1.48)
Male Gender	0.93 (0.69–1.25)	0.93 (0.69–1.25)
Age (1 Year)	0.99 (0.98–1.00)	0.99 (0.99–1.00)
Public Location	2.23 (1.55–3.22)	2.20 (1.53–3.18)
Witnessed Arrest		
Bystander	2.39 (1.64–3.50)	2.68 (1.86–3.86)
EMS	2.91 (2.01–4.22)	2.90 (2.00–4.19)
Bystander Resuscitation		
Any	1.11 (0.80–1.54)	1.05 (0.75–1.48)
CPR Attempted	0.88 (0.64–1.22)	0.48 (0.11–2.04)
AED Applied	0.98 (0.83–1.17)	2.98 (1.31–6.79)
AED Shocks	0.72 (0.40–1.28)	21.99 (1.22–396.98)
EMS Response Time (1 Minute)	0.89 (0.83–0.94)	0.88 (0.83–0.94)

Table 3.3: Odds ratios and 95% confidence intervals from each of the univariate predictor analyses.

create univariate composite point estimates and confidence intervals for each covariate. The results from these analyses are displayed in Table 3.3. The results from each model are also illustrated graphically along with previously-published complete case analyses in the Forest plot in Figure 3.2.

3.5 Complete Case Analysis

The second stage of our analysis was the examination of only "complete" cases (n=4,725) which had ascertainment of all examined covariates. This step functioned as a validation of our imputation model. Row-wise deletion of incomplete cases was used to generate a subset of the data which could be subjected to all subsequent analysis steps without encountering censored data.

Univariate Analysis

In univariate analysis of these complete cases, each of the covariates were tested as predictors for survival to hospital discharge in separate univariate logistic regression models. The results from these analyses are displayed in Table 3.3 alongside the imputed data results and are illustrated graphically along with previously-published complete case analyses in the Forest plot in Figure 3.2.

Multivariate Analysis

In multivariate analysis of these complete cases, each of the covariates were added as predictors for survival to hospital discharge in a multivariate logistic regression model. The results from this analysis are displayed in Table 3.5 and are again illustrated graphically along with previously-published complete case analyses in the Forest plot in Figure 3.2.

Table 3.4: Odds ratios and 95% confidence intervals from each of the multivariate predictor analyses.

Covariate	Consensus Model Imputed Cases	Consensus Model Complete Cases	Expanded Model Imputed Cases	Expanded Model Complete Cases
Shocks	0.82 (0.56–1.21)	0.87 (0.53–1.42)	0.82 (0.56–1.21)	1.12 (0.57–2.22)
Male Gender	0.91 (0.66–1.24)	0.71 (0.47–1.06)	0.91 (0.66–1.24)	0.77 (0.42–1.41)
Age (10 Years)	0.99 (0.98–1.00)	0.99 (0.98–1.01)	0.99 (0.98–1.00)	1.00 (0.98–1.02)
Public Location	1.92 (1.30–2.84)	3.03 (1.93–4.78)	1.91 (1.29–2.83)	2.95 (1.52–5.73)
Witnessed Arrest				
Bystander	2.40 (1.59–3.61)	2.76 (1.80–4.23)	2.41 (1.60–3.64)	2.53 (1.29–4.97)
EMS	2.88 (1.75–4.76)	N/A[a]	2.84 (1.72–4.68)	N/A[a]
Bystander Resuscitation				
Any	1.13 (0.77–1.66)	1.15 (0.76–1.72)	–	–
CPR Attempted	–	–	0.22 (0.06–0.78)	0.50 (0.11–2.37)
AED Applied	–	–	2.10 (1.06–4.15)	1.76 (0.70–4.42)
AED Shocks	–	–	1.41 (0.59–3.38)	N/A[a]
EMS Response Interval (1 Minute)	0.96 (0.90–1.03)	0.98 (0.91–1.05)	0.96 (0.90–1.03)	0.95 (0.85–1.06)

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Table 3.4 – continued from previous page

Covariate	Consensus Model		Expanded Model	
	Imputed Cases	Complete Cases	Imputed Cases	Complete Cases
ROC Site				
1	1.00	1.00	1.00	1.00
2	1.27 (0.69–2.36)	1.52 (0.70–3.32)	1.29 (0.69–2.40)	1.39 (0.51–3.76)
3	1.07 (0.57–2.02)	1.01 (0.46–2.21)	1.08 (0.57-2.03)	0.73 (0.21–2.54)
4	0.19 (0.04–0.84)	0.30 (0.04–2.42)	0.19 (0.04–0.81)	0.44 (0.05–3.95)
5	0.85 (0.44–1.65)	0.67 (0.24–1.88)	0.86 (0.44–1.69)	0.21 (0.02–1.80)
6	0.57 (0.30–1.07)	0.62 (0.29–1.33)	0.56 (0.30–1.06)	0.55 (0.20–1.55)
7	0.85 (0.41–1.76)	0.62 (0.21–1.86)	0.82 (0.39–1.70)	0.20 (0.02–1.75)
8	0.58 (0.31–1.07)	0.47 (0.21–1.02)	0.57 (0.31–1.06)	0.53 (0.18–1.53)

[a] Incomputable due to failure of convergence caused by quasi-complete separation.

3.6 Model Diagnostics

Standard model diagnostics for logistic regression were employed. For each of the imputed datasets, the model fit diagnostics indicate a good fit of the model. The Hosmer-Lemeshow Goodness-of-Fit chi-square tests all show insignificant p-values therefore we declare the model to be well calibrated for these data. Similarly, the area under the Receiver Operating Characteristic curves were calculated and a representative example is displayed in Figure 3.3. These diagnostics consistently indicate that our models have adequate prediction capability.

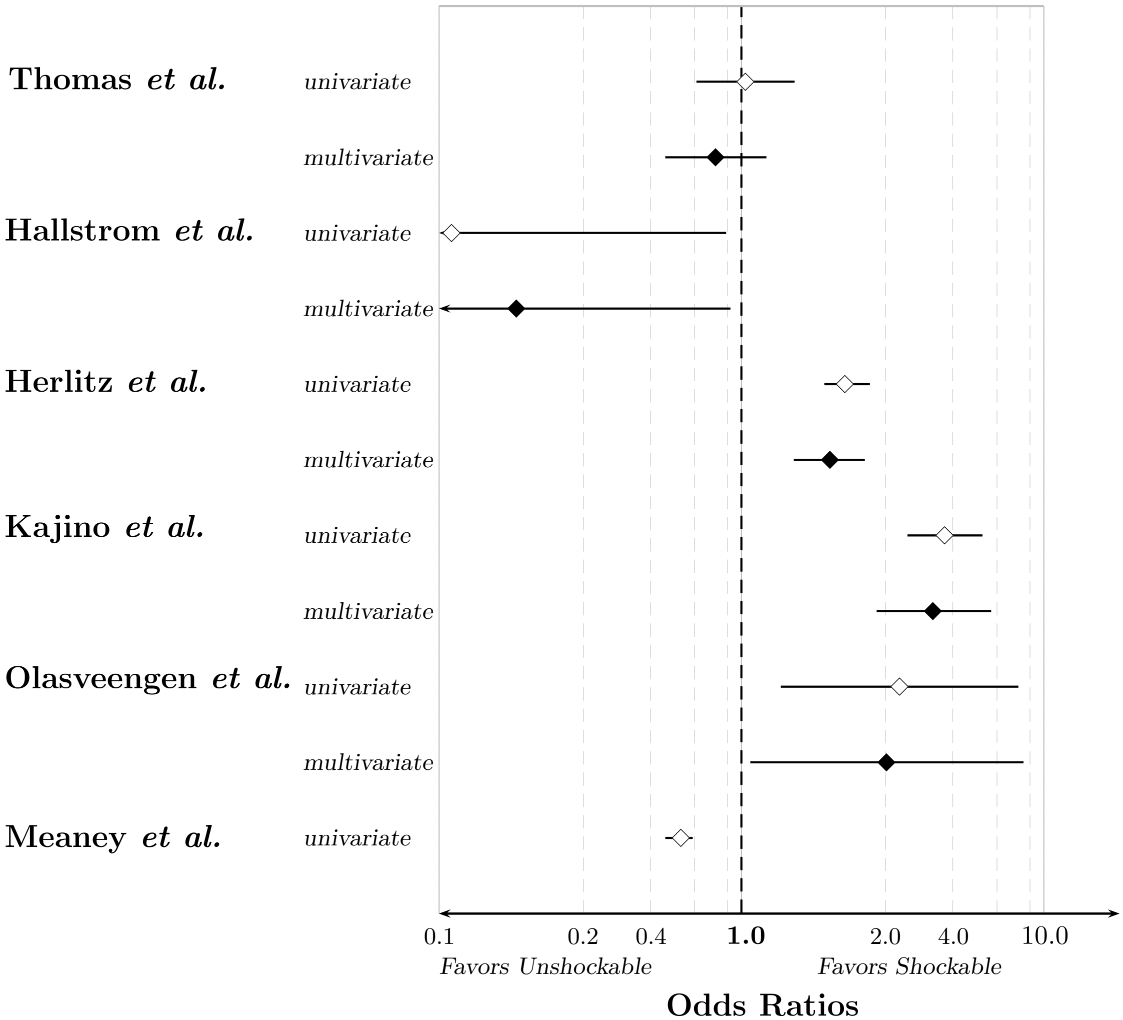

Figure 3.2: Forest plot of prior univariate and complete-case multivariate analyses with results from our univariate and multivariate consensus model analyses.

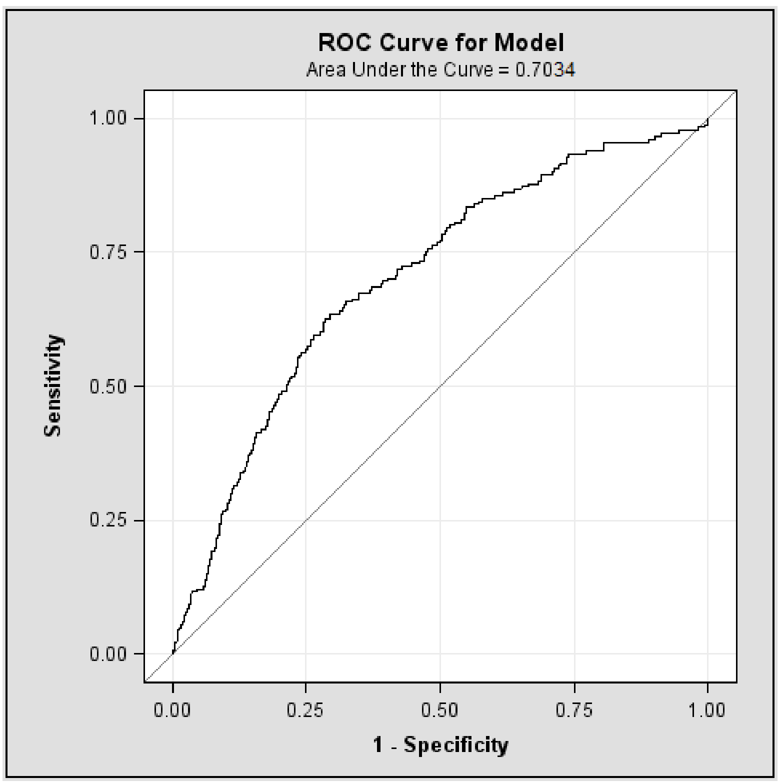

Figure 3.3: A Receiver Operating Characteristic (ROC) curve representative of the expanded model.

Chapter 4

Discussion

4.1 Past Evidence

The lead authors on the four out-of-hospital papers (Herlitz, Kajino, Olasveengen, and Hallstrom) came together in 2010 and offered a commentary in Resuscitation on their contradictory findings. They agreed that for a variety of factors in the communities they examined, that the true answer to the question likely lay somewhere in the middle. They agreed that "the 'true' rates probably lie somewhere in between and will likely be center specific due to differing criteria for attempting CPR, different treatment protocols and response time differentials, and possibly due to different community practices such as use of beta-blockade, etc." Their proposition is consistent with our findings.[8]

4.2 Summary of Results

Our analysis found no statistically significant relationship, neither protection nor harm, between conversion from initially non-shockable rhythms to subsequent shockable rhythms in terms of survival to hospital discharge. Whether analysis was limited to only complete cases or broadened to include all cases with the help of multiple imputation there was no significant change in our findings. The addition of multiple covariates to the model, known from previous studies to be significant confounders, also had no significant effect on our estimate of the effect of subsequent rhythm conversion on survival to hospital discharge. The relative degree of uncertainty, as seen in the width of our confidence intervals, experienced in many of our results suggest that other potentially unmeasured factors (including patient, environmental, prehospital, and in-hospital factors) which were not accounted for in our models may be responsible for the observed variation.[5]

These investigators were surprised to discover that the provision of bystander CPR was not predictive of survival to hospital discharge in our study. Past studies have identified this as an important factor for survival although relatively few studies have examined this question exclusively in the non-shockable subset of cardiac arrests.[12,32]

Ultimately, quasi-complete separation was a problem for several of the variables (e.g. – EMS Witnessed & AED shocked) resulting in nonconvergence even when Firths' procedure was used. For this reason they were removed from the analysis when necessary.

4.3 Potential Limitations

Considerable discussion of the limitations potentially inherent in the ROC Epistry data have been previously published. These are prospecively collected data from a multi-site sample of culturally similar communities. Each community has distinct 911 procedures including dispatcher CPR instructions and dispatched responses. They all differ in their individual response unit capabilities, their prevalence of AED use, and their CPR quality measures. Additionally, each community differs in their termination of resuscitation guidelines, transport procedures, and in-hospital care capabilities. Nonetheless, they all share more in common with one-another than with some of the sites represented by previous studies (e.g. - Sweden and Japan).

Another limitation of these ROC Epistry data is due to the delayed nature of some of the data collection. While prehospital care was often provided by bystanders who performed CPR and/or AED care which was only documented by the subsequently-arriving EMS crews. These data were often not evaluable by ROC researchers beyond what EMS reported in their charts.

Also of note in this particular dataset is the fact that two ROC-participating sites opted not to include their data for local analyses such as this one. Together, these sites accounted for 27.1% of the total population and 35.0% of all cardiac arrests occurring in the Resuscitation Outcomes Consortium during this time period. These two sites also represented 35.5% of nonshockable cardiac arrests which is a substantial enough portion to suggest that if their distributions of survival in nonshockable rhythms differed from those communities represented in these data that their inclusion might have shifted our point estimate significantly in either direction.

An interesting limitation which was pointed out by another ROC investigator was the possibility that crews could have provided unsynchronized countershocks (i.e. – defibrillations) to patients who never converted to shockable rhythms as a "last ditch" effort before terminating resuscitation (the presumed outcome in cases like these). These would always be nonshockable patients in the NO SHOCK group (on account of their sustained nonshockable status) misclassified to the SHOCK group. This presumably rare event could potentially bias our results toward survival in the NO SHOCK group as it would increase the proportion of mortality in the SHOCK group. Without continuous ECG Rhythm analysis (which are unavailable in these data) we are unable to accurately quantify the magnitude of this potential bias. It is likely that the number of cases in our data where this occurred are few as A) this course of treatment (i.e. - defibrillating unshockable rhythms) is not recommended by the American Heart Association or the International Liason Committee on Resuscitation, and B) the ROC site represented by this particular ROC investigator did not elect to share its data with the Epistry local dataset.

Additionally, no data are available in our dataset to describe either CPR process quality or post-resuscitation care efforts either in the prehospital or in-hospital environments. In particular, measures of CPR quality have been shown to predict survival from cardiac arrests and this would therefore have been desirable to control for in our study.

One unique strength of our study is the diversity of the communities and EMS Systems involved including differences in rurality, EMS organizational structures, and patient population characteristics. This makes our results very comparable to the original Hallstrom paper which also shared a similarly diverse population.

4.3.1 Misclassification Bias

Misclassification bias can exist in several forms. First, there is the potential of misclassification bias resulting from miclassifying cases of subsequent shocks as no shocks or the converse, either of which would bias findings toward the null by diluting differences between the two groups. Another concerning misclassification is that of misidentifying shockable rhythms as nonshockable in the initial rhythm category as nonshockable cases were intended to be excluded altogether and their survival is anticipated to be much higher than either of the nonshockable groups. Neither of these possible misclassifications is considered to be frequent in these data as trained ROC staff carefully analyzed the data files from the monitors and AEDs used during each of these cardiac arrests. These devices record continuous waveform ECG data as well as the energy and timing of any countershocks delivered.

4.3.2 Other Sources of Bias

There is the potential for biases in these data from sources of variation which were not identified or collected. On occasion, there may be variation caused by factors which have not been considered however this is believed to be a small factor as the collection of out-of-hospital cardiac arrest data is governed by the well-established consensus-based Utstein criteria which have been carefully written in

4.4 Future Studies

These findings suggest the importance of an emphasis on etiology of cardiac arrest (and perhaps also by precipitating events) in future studies. As was noted earlier, the prior study by Meaney *et al.* did take place in the in-hospital setting where both etiology and precipitating events are likely to differ from those experienced by responders in the out-of-hospital setting. If future investigators are able to carefully segregate cardiac arrest cases by etiology we may be in a better position to adequately describe the relationship between subsequent shocks and cardiac arrest survival.

Another important focus for future research would be the care provided on-scene prior to determination of death. As we proposed in this paper it would be wise to consider declaration of death prior to completion of adequate ACLS measures as a potential exclusion criteria in future studies. Whereas most of the localities represented in these data do allow declaration of death by field EMS providers, at least one locality represented in prior literature (Kajino *et al.*) did not allow field termination of resuscitation which may potentially have affected the results of that study.

4.5 Implications

As has been previously alluded to by other investigators, the issue of whether subsequently shocked patients who present in unshockable cardiac arrests is a murky one. Previous investigators have suggested that the true answer likely falls somewhere between the findings of their prior research. Our investigation found exactly that. Despite a relatively large sample size, satisfactorily complete records for both the primary predictor and outcome as well as for the covariates used in multivariate analysis, and a statistically rigorous multiple imputation procedure to allow complete case ascertainment in the analyses, we were unable to detect any statistically significant difference in outcome between those who were subsequently shocked and those who remained in unshockable rhythms. Moreover, our analysis did not find sufficient differences between these two groups to even suggest that such a difference was likely to be uncovered were more data made available to us.

There are several plausible explanations for these findings as previously discussed however these investigators feel that the most likely explanation may simply be the fact that not all nonshockable rhythms are alike. There is likely to be a dichotomy of response to subsequent shocks whereby one subset of causes for nonshockable arrests displays improved survival when subsequently shocked while another subset displays diminshed survival with subsequent shocks. Together, if distributed in roughly equal proportions (or with unequal proportions but with similarly unequal magnitudes) these subsets of causes will cancel one another out resulting in minimal overall effect. Our findings would be consistent with this hypothesis.

As previously discussed, our findings emphasize the importance of considering etiology of cardiac arrest in future studies. The logistical challenges of that achieving that goal are significant and will potentially require new research methods to accomplish with a high degree of certainty. Nonetheless, the benefits to the goal of understanding cardiac arrest and resuscitation will be substantial.

One important message to take away from this investigation is that while the prognosis for survival from nonshockable rhythms is not as positive as it is for initially shockable rhythms, it is possible for patients presenting with these rhythms to be successfully resuscitated. Moreover, neither does it appear that converting from nonshockable to shockable cardiac arrest rhythms is a reliable indicator of improving prognosis nor is the lack of this conversion the death sentence that it is sometimes believed to be. For this reason we suggest that it is important to give every patient found in nonshockable rhythms (barring extenuating circumstances) the benefit of the doubt and aggressively perform CPR and ACLS resuscitation until all efforts have been exhausted. From our research we argue that conversion from nonshockable presenting rhythm itself is not a strong enough indicator to alter resuscitation efforts or methods.

Chapter 5

Conclusions

We found no significant evidence to support the argument that conversion from non-shockable to shockable arrhythmias during the course of resuscitation is prognostic for the patient's outcome. We feel that this is because non-shockable arrests have diverse etiology and some may both benefit while others may suffer from the early introduction of defibrillation therapy. A strong focus on cardiac arrest etiology is needed in future research in order settle this debate. In the meantime we feel that it is premature to make any treatment-related decisions on the basis of this poorly-prognostic indicator of survival.

Appendix A

Strategies for Addressing Missing Data

A.1 Background

All too often in research data cannot be completely ascertained – whether it is due to subject choice, technical failure or even human error, or even systematic design flaws in the study itself. When researchers encounter missing data they have several choices as to how best to handle them. Perhaps the first choice is to discard cases which do not have complete ascertainment and limit analysis to only the complete cases. However, this method is undesirable for several reasons. If the study is powered to identify a particular effect size with the available sample, excluding incomplete cases will reduce the effective sample size and thereby reducing study power to discern the desired effect size. Additionally, particularly of concern for multivariate analyses – complete case analysis can introduce biases if the missing data occur in patterns or they are dependent on the missing values themselves.[44,45]

Modern statistical methods have introduced several techniques for managing incomplete data. The selection of specific technique however requires careful consideration of the features of the data, particularly the missing data. The characteristics of missing data, known as the data's missingness, may limit the investigator's options with regard to handling the missing data.

Patterns of missingness can be described in three ways. The data can be missing completely at random (MCAR) which requires that whether or not a variable is missing cannot be associated with any other features of the data. This is a particularly difficult criteria to satisfy if for no other reason than statistically significant associations between normally-distributed data will occur by chance alone 5% of the time (for alpha = 0.05 significance levels) and multivariate models often have numerous variables with missing observations, each a chance for an association to occur by chance. A less restrictive criteria is that of missing at random (MAR) which stipulates that a variable's missingness cannot be associated with levels of the variable itself. The last pattern of missingness is that of missing not at random (MNAR) whereby the level of the variable itself is correlated to its missingness. This is often the case when private information, such as income level, is omitted from a survey response when the respondent feels they sit on one extreme or the other.[45]

While MCAR is difficult to satisfy, MAR is much more common. Unfortunately however there is no statistical test which can confirm the presence of MAR data and therefore investigators must assert that their data is satisfies MAR in the form of a statistical assumption. Although MNAR missingness is common, it is often a simple matter to intellectually identify its potential. If MNAR cannot be identified then MAR is typically assumed.[45]

The simplest method of handling missing data is to exclude the missing records in a procedure called complete case analysis. If MCAR missingness can be established then the complete case analysis can be assumed to be accurate. Unfortunately, MCAR is difficult to identify and relatively rare and complete case analyses of even MAR data can yield severely biased results.

If MAR data are identified there are other options for analysis of the missing data. Among these options are imputation, likelihood based methods. At its most basic, imputation is simply the process of estimating or inferring the values of missing observations. This can be done with regard to the distribution of known values for a given variable or on a much more sophisticated level the distribution of known values for a variable conditional on the other variables for that observation. In maximum likelihood estimation, the missing values are compensated for in the analysis by seeking the parameter value which maximizes the log-likelihood of the parameter of interest.[45,46]

The remainder of this appendix will focus on the topic of imputation.

A.2 Multiple Imputation

As described above, single imputation is the process of estimating missing values where only one estimate of each missing value is generated. The algorithm used for estimating these missing values can range from simply substituting the mean or median (which tends to severely bias the results toward the null hypothesis) to using complex regression models to compute the probabilistic best guess for each missing value. All of these single imputation methods however are prone to introducing bias and decreasing variance and for these reasons this is not a particularly popular approach among researchers.[46,47]

However by repeating the imputation process multiple times and taking steps to ensure the imputed values are carefully drawn from the appropriate distribution it has been shown that these imputed values can closely mimic the distribution of the actual missing values. It is important to understand that these imputed (or substituted) values are not believed to be the missing values but are simply meant to accurately represent the distribution of those missing values and thus allow interpretation of the incomplete data to while possessing only a minimal risk of introducing bias. This can be shown to be true even when a fairly large fraction of the data are missing.[46,48,49]

A.2.1 Assumptions for Imputation

The procedures involved in multiple imputation operate in the assumption that the continuous data represent a multivariate normal population distribution and the missing values can occur for any of the variables. The MI procedures also assumes that the data are at least missing at random (MAR) where the probability of missingness is not affected by the value of the missing variable. Unfortunately, the MAR assumption cannot be mathematically verified from the data at hand and the researcher must be careful to consider the possibility that the missing data may be missing not at random (MNAR) before asserting to the contrary.[46]

A.2.2 Methods of Imputation

Some of the earliest methods for imputation were very rudimentary. As described above, merely substituting the mean or median value for a variable introduced a strong bias toward null. Another technique used most often in longitudinal studies is known as last observation carried forward whereby the investigator simply substitutes the last observation from the same observational unit for the missing value. A close relative uses an interpolated linear or exponential value to replace missing values between two known values of the same observational unit.[47]

Another method known as hot deck imputation was popular for a long time. In hot deck imputation, values were replaced by a previously-observed value from within a "hot" deck of similar observations within the same dataset. A later counterpart known as "cold" deck imputation performed a similar technique but with known values from a previously-acquired reference dataset not involved in the analysis. All of these methods fell out of favor for several reasons including the tendancy to bias toward the null and reduce overall variance.[= * ore recently, sophisticated methods of inference have been developed using the framework of bayesian statistics. The MI procedure employed by SAS and similar procedures employed by other software uses a Markov-Chain Monte Carlo method where a single chain is used to create the desired number of imputations.[51] nother frequently-selected method for imputing missing data are selected by a sequence of regression analyses. There are several variations on the regression analysis form of imputation but one which is commonly used is that employed by the IVEware software as described by Raghunathan *et al.*. This technique employs a series of regressions being linear, logistic, Poisson, generalized logit or a combination dependent on the data type being imputed. These data types are then categorized as continuous, binary, polytomous categoÂrical, count, or mixed. In several rounds, the regression proceeds first with the variable with the least number of missing values. Then subsequent regressions are conducted using the newly imputed values. This regression sequence is repeated until stable values of imputations are reached. This procedure can also be modified to incorporate bounded and otherwise restricted variables.[52–55] Iterations and Imputations here has been much debate about the correct number of imputations to achieve statistical reliability in estimating missing data. Relative efficiency of imputation is estimated by the function in the equation below. For most cases of multiple imputation if up to 50% of data are censored and if 10 imputations are used, the imputer can achieve a high level ($\geq$ 95%) of relative efficiency. Efficiency decreases with fewer imputations and great degrees of missing data.[46]

$$r.e. = (1 + \frac{\lambda}{m})^{-1}$$

Figure A.1: The formula for calculating relative efficiency (r.e.) of a multiple imputation where λ is the proportion of missing data and m is the number of imputations.

A.3 Imputation Models

The variable model used for conducting the imputation should in principle be the same model used for the resulting analysis. However evaluation of this principle has revealed that, despite there being some consequences, the expansion of the imputation model to include other relevant variables may actually improve the quality of the imputation process. The consequences of conducting an analysis with a simpler model than that used for imputation are potentially missing the relationships between imputed variables and non-imputed variables in the model. In other words, if there is no relationship between any of the analyzed variables and any of the other imputed variables then the models are functionally equivalent.

A.4 Analysis of Imputations

Each of the datasets produced by a multiple imputation procedures must be analyzed itself. The parameter estimates resulting from these analyses are then combined with the estimates from each of the other imputation datasets to create the final parameter estimates of the imputed data as a whole. The point estimates are combined simply as the arithmetic mean of the respective single-dataset point estimates. The variance however is computed by combining the within-dataset and the between-dataset variances in accordance with the somewhat complex series of equations seen below.

$$\begin{aligned}
\hat{U}_m &= \frac{1}{m}\Sigma U_i && \text{Within-Imputation Variance} \\
\hat{B}_m &= \frac{1}{(m-1)}\Sigma(Q_i - Q_m)^2 && \text{Between-Imputation Variance} \\
\hat{T}_m &= \hat{U}_m + (1+\frac{1}{m})\hat{B}_m && \text{Total Variance}
\end{aligned}$$

Figure A.2: The procedure for calculating overall variance of an imputation.

The confidence intervals are then generated using the following equations where t_v follows Student's t-distribution with v degrees of freedom and where $\hat{Q}_m$ represents the mean point estimate of the individual imputations.

$$\begin{aligned}
\hat{U}_m \pm & \quad t_v(\frac{\alpha}{2})T_m^(\frac{1}{2}) \\
v = & \quad (m-1)[1+\frac{\hat{U}}{(1+\frac{1}{m})B_m}]
\end{aligned}$$

Figure A.3: The procedure for calculating confidence intervals from an imputation.

Appendix B

Acronyms

ACLS	Advanced Cardiac Life Support
AED	Automated External Defibrillator
	Semiautomated External Defibrillator (SAED)
AHA	American Heart Association
AICD	Automated Implantable Cardioverter-Defibrillator
ALS	Advanced Life Support
CCA	Complete Case Analysis
CPR	Cardiopulmonary Resuscitation
DCC	Data Coordinating Center
DNR	Do Not Resuscitate
	Do Not Attempt Resuscitation (DNAR)
EKG	Electrocardiogram (German: Kardio, aka ECG)
EMS	Emergency Medical Services
EMT	Emergency Medical Technician
EMT-B	Emergency Medical Technician-Basic
EMT-I	Emergency Medical Technician-Intermediate
EMT-P	Emergency Medical Technician-Paramedic (aka Paramedic)
ILCOR	International Liason Committee on Resuscitation
IRB	Institutional Review Board
MAR	Missing at Random
MCAR	Missing Completely at Random
MI	Multiple Imputation
MNAR	Missing Not at Random
OHCA	Out of Hospital Cardiac Arrest (also OOHCA)
PEA	Pulseless Electrical Activity
ROC	Resuscitation Outcomes Consortium
	also Receiver Operating Characteristic "curve" (disambiguation)
ROSC	Return of Spontaneous Circulation
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

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